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Fluctuations of Radial Artery Distensibility Throughout the Menstrual Cycle

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Abstract—Estrogen administration has a number of favorable cardiovascular effects, and recent evidence suggests that these include an increase in arterial distensibility. Whether this is also the case for the physiological changes in estrogen production during the menstrual cycle has never been determined, however. In 21 premenopausal healthy women, we continuously measured radial artery diameter and blood pressure by an echo-tracking device and a beat-to-beat finger device, respectively. Arterial distensibility was calculated as distensibility/blood pressure curve. The measurements were made during the follicular, ovulatory, and luteal phases of the menstrual cycle. As expected, compared with the follicular phase, plasma estradiol, follicle-stimulating hormone, luteinizing hormone, and prolactin were increased in the ovulatory phase, whereas progesterone was increased in the luteal phase, together with antidiuretic hormone. Radial artery distensibility was increased in the ovulatory and reduced in the luteal phase, the changes being independent of the small, concomitant blood pressure changes. The arterial wall stiffening seen in the luteal phase was associated with a reduction in the flow-dependent endothelial dilatation of the radial artery as assessed by the hyperemia after short-term ischemia of the hand. Thus, the natural menstrual cycle is characterized by alterations in radial artery distensibility. The mechanisms responsible for this phenomenon remain to be clarified. It is possible, however, that the greater arterial distensibility of the ovulatory phase is due to an estrogen-dependent reduction in vascular smooth muscle tone, whereas the arterial stiffening of the luteal phase depends on vascular smooth muscle contraction due to more complex hormonal phenomena, ie, an endothelial impairment due to estrogen reduction but also to an increase in progesterone and antidiuretic hormone levels. (Arterioscler Thromb Vasc Biol. 1999;19:1925-1929.)

Key Words: arterial distensibility • blood vessels • estrogens • physiological hormonal variations

Estrogens are believed to provide protection against cardiovascular disease, and evidence exists that they have a number of favorable cardiovascular effects, ie, dilatation of coronary and systemic arterioles, improvement of endothelial function, inhibition of fibroblast and vascular smooth muscle cell proliferation, and inhibition of collagen accumulation in the aortic wall. Moreover, several studies suggest that another favorable cardiovascular effect of estrogens is an increase in arterial distensibility.

Estrogen production undergoes major changes during the menstrual cycle, providing a suitable setting for more directly examining the physiological effects of estrogens on cardiovascular variables and functions. In the present study, we have made use of this setting to examine the physiological effect of estrogen on arterial distensibility as assessed in the radial artery. We have also studied the flow-dependent changes in radial artery diameter throughout the menstrual cycle to see whether any such effect could be accounted for by an alteration in endothelial function.

Methods

We studied 21 women with an age ranging from 23 to 41 years (mean±SEM, 27.8±1.1 years). All subjects had a sphygmomanometric blood pressure <140/90 mm Hg at 2 visits performed in the outpatient clinics. Women were selected if they had (1) no history of cardiovascular or gynecological diseases, (2) no physical or laboratory evidence of organ dysfunction or structural abnormalities, and (3) no use of oral contraceptives. On specific questioning, all women reported no smoking habits and no excessive alcohol consumption. All women volunteered their participation in the study after being informed of its nature and purpose. The study protocol was approved by the ethics committees of the institutions involved.

Measurements

Radial artery diameter was measured by an A-mode ultrasonic device (NIUS 02, Omega). In brief, a highly focalized transducer operating at a frequency of 10 MHz was stereotactically positioned over the radial artery 2 to 4 cm above the wrist, direct contact with the skin being prevented by use of a gel as a medium. With the subject supine and the arm immobile at heart level, the transducer was oriented perpendicular to the longitudinal axis of the vessel on the basis of the acoustic Doppler signal. The backscattered echoes from the inner posterior and anterior walls of the artery were
visualized on the computer screen and electronically digitized (via an analog/digital fast transducer) to allow internal diameter variations to be derived at 50 Hz. The spatial resolution during the blood pressure cycle was 0.0025 mm.16,17 The device also made use of a photoplethysmographic system (Finapres 2003, Ohmeda), which allowed blood pressure to be recorded at 50 Hz from a finger ipsilateral to the radial artery examined, with an accuracy similar to that of intra-arterial blood pressure recording18 and a resolution of 2 mm Hg.19 The concomitant acquisition of continuous arterial diameter and blood pressure signals allowed us to calculate the diameter-pressure curve of the vessel.19 The curve was then analyzed according to its best fit with the arctangent model of Langewouters, which is based on the following formula:

\[ S = \alpha \left( \frac{\pi}{2} - \tan^{-1} \left( \frac{P - \beta}{\gamma} \right) \right) \]

where \( S \) is the cross-sectional area; \( P \) is blood pressure; and \( \alpha, \beta, \) and \( \gamma \) are 3 optimal parameters describing the spatial position of the diameter-pressure curve.19 From this formula, cross-sectional compliance \( (C = \Delta S/\Delta P) \) was calculated as follows:

\[ C = \frac{\alpha}{\gamma} \left( 1 + \left( \frac{P - \beta}{\gamma} \right)^2 \right)^{-1} \]

Compliance values were corrected for cross-sectional areas of the vessel to obtain cross-sectional distensibility \((D)\) according to the formula\(^{19} \) \( D = C/S. \) Cross-sectional distensibility was expressed as consecutive values from diastole to systole, ie, as a distensibility-pressure curve. All measurements were made by a single operator unaware of the study design. The within-operator CV of diastolic radial artery diameter (see below) of measurements performed over a 1-month interval in our laboratory was 4%.

In each woman, plasma \( 17\beta \)-estradiol, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin were measured by standard radioimmunoassays\(^{21} \) from the venous blood sample taken from an antecubital vein. Plasma osmolarity was also measured from the antecubital vein blood sample. In 12 women, these measurements were complemented by radioimmunoassay measurements of antidiuretic hormone (ADH), also from venous blood samples.

Protocol and Data Analysis

All women were studied in 3 phases of their menstrual cycle, ie, (1) days 5 to 7 (follicular phase), (2) days 13 to 15 (ovulatory phase), and (3) days 21 to 29 (luteal phase). The duration of the menstrual cycle ranged from 23 to 34 days. The entry into the study was randomized so that in 7 women it was the follicular phase; in 7, the ovulatory phase; and in 7, the luteal phase. All hemodynamic and hormonal measurements were made in the afternoon (after a 24-hour abstinence from alcohol and caffeine consumption) according to the following protocol.

1. The subject was placed in the supine position and fitted with the finger blood pressure and echo-tracking devices. (2) After a 15-minute rest, blood pressure, heart rate, radial artery diameter, and cross-sectional distensibility were continuously measured for 15 minutes in the left forearm. (3) After a 30-minute rest, blood for hormonal measurements was withdrawn.

In 9 subjects, the aforementioned protocol was modified by also investigating endothelial function during the different phases of the menstrual cycle. To this aim, steps 1 and 2 were followed by a 4-minute exclusion of circulation to the hand via inflation of a pediatric-type cuff positioned around the wrist to suprasystolic pressure values. Blood pressure, heart rate, and radial artery diameter were measured continuously over the 5-minute hyperemia immediately after cuff deflation. Radial artery blood flow velocity was concomitantly obtained by a transducer operating at a frequency of 8 MHz (Doptek 2003, Omega), stereotaxically positioned 40° to 60° on the basis of the acoustic Doppler signal at the same vessel site from which diameter had been measured. Arterial blood flow was calculated automatically as the product of flow velocity and cross-sectional area values. It has been shown that the pressure–flow relationship is linear in human radial arteries.20,21

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Ischemic period, increases in radial artery diameter are abolished by the administration of substances such as \( N \)-nitro-\( \ell \)-arginine methyl ester, which means that this phenomenon depends on a flow-mediated increase in nitric oxide release.22

During the baseline period (step 2 of the protocol), individual diameter–blood pressure and cross-sectional distensibility–blood pressure curves were derived from 30-second periods taken at 3-minute intervals during the 15 minutes of continuous measurement. During the hyperemic period, blood pressure, arterial diameter, and blood flow were derived from the 10-second period during which diameter and/or flow values were maximal (usually within the first minute after release of the inflated cuff). Data were summed and expressed as mean diameter and distensibility curves for the group as a whole. This procedure also was done for (1) radial artery diameter at the diastolic blood pressure value; (2) the integral of the area under the curve that relates cross-sectional distensibility to blood pressure divided by pulse pressure, ie, for the difference between systolic and diastolic blood pressures. This provided a single, comprehensive, and normalized value for arterial distensibility ("distensibility index"; see References 23 through 26) for statistical comparisons between different experimental sessions; and (3) blood pressure,
blood flow, and heart rate. Mean±SEM values for the group as a whole were also obtained for hormonal and plasma osmolarity data. The statistical significance of the differences between the 3 phases of the menstrual cycle was assessed by 1-way ANOVA for repeated measurements. Student’s 2-tailed t test for paired observations and the Bonferroni correction for multiple comparisons were used to identify the differences. A value of P<0.05 was taken as the level of statistical significance.

Results

Figure 1 shows the hormonal values in the 3 phases of the menstrual cycle. Compared with the follicular phase, the ovulatory phase showed, as expected, an increase in 17β-estradiol, LH, FSH, and prolactin, whereas the luteal phase showed a marked increase in progesterone, a return of 17β-estradiol, FSH, prolactin, and LH to the values of the follicular phase, and an increase of ADH values. Osmolarity in the 3 phases was 272.7±3.6, 274.4±1.8, and 273.8±1.7 mmol/L, respectively. Systolic and diastolic blood pressures (Figure 1, upper panels) showed a slight increase in the luteal phase, while heart rate remained unchanged throughout (71±2, 72±2, and 73±3 bpm, respectively).

The radial artery data are shown in Figure 2. In all 3 phases of the menstrual cycle, radial artery diameter increased progressively and slightly as blood pressure increased from diastole to systole, whereas radial artery distensibility showed a concomitant marked and curvilinear reduction. In the follicular phase, diastolic radial artery diameter was slightly but not significantly greater than that in the other 2 phases. Radial artery distensibility was markedly reduced in the luteal compared with the other 2 phases. The reduction was evident throughout the diastolic-systolic pressure range and also clearcut in the isobaric portion of the distensibility curve, ie, the portion of the curve at which pressure values overlapped in the 3 phases. When quantified as distensibility index, the reduction (versus the ovulatory phase) amounted to 40%.

Figure 3 shows the data obtained in the hyperemic period after 4-minute ischemia of the hand. Compared with preischemic values, this period showed no change in blood pressure and heart rate, a marked and significant increase in radial artery blood flow, and a significant increase in radial artery diameter. The increase in blood flow was similar in the 3 phases of the menstrual cycle, whereas the increase in arterial diameter was significantly less in the luteal (+4%) compared with the follicular (+11%) and ovulatory (+13%) phases (P<0.05).

Discussion

The present study provides the first observation in humans that arterial mechanical properties undergo noticeable variations during the menstrual cycle; ie, that arterial distensibility is greater during the ovulatory phase but less during the luteal phase. It also provides evidence that this variation occurs together with the hormonal changes typical of the menstrual cycle, which suggests this phenomenon to be dependent on sex hormones.

The mechanisms by which hormonal fluctuations occurring during the menstrual cycle affect arterial distensibility are not explained by our findings. Animal studies, however, have shown that (1) vascular smooth muscle cells have estrogen receptors; (2) estrogen administration has direct vasodilatory effects; (3) both estrogen administration and the increase in estrogen production during pregnancy flatten the pressure-volume relationship of the large arterial reservoir and reduce the pulse wave velocity throughout the arterial tree in a fashion that indicates an increase in arterial distensibility; and (4) an increase in arterial distensibility and/or vasodilatation characterizes both human pregnancy and transsexual individuals subjected to administration of high dose of exogenous estrogens. Taken together, these findings suggest that in the follicular phase, arteries are
made more distensible by a physiological increase in estrogen levels, presumably because this increase leads to the relaxation of smooth muscle in the arterial wall, given that the elastic modulus is less for relaxed than for contracted muscle tissue.20 These data may also suggest, conversely, that the arterial stiffening occurring in the luteal phase is due to an increase in vascular smooth muscle contraction due to a physiological reduction in estrogen levels. It seems clear from our data, however, that this latter phenomenon is mechanistically more complex. First, in the luteal phase, nitric oxide–dependent modulation of arterial diameter was reduced, suggesting that an increase in smooth muscle contraction could also originate from endothelial dysfunction, although the existence of estrogen receptors in endothelial cells makes it possible that this dysfunction is also related to a reduction in estrogen levels. Second, the luteal phase was additionally characterized by a marked reduction in FSH, LH, and prolactin and by a marked increase in progesterone and ADH levels. Some of these hormones have a clear-cut ability to cause vascular smooth muscle contraction and sodium and water retention, which suggests their participation in arterial stiffening either by reinforcing the effect of a reduction in estrogens or by “waterlogging” the vascular wall. The nonestrogenic contribution to the luteal phase–associated reduction in arterial distensibility may account for the fact that arterial distensibility was greater in the follicular than in the luteal phase, despite similar estrogen levels during both phases.

A few other points should be mentioned. One, in the luteal phase, arterial blood pressure was slightly increased compared with the previous 2 phases. This increment was not responsible for the concomitant reduction of arterial distensibility, however, because this reduction was also manifest under isobaric conditions, ie, at identical blood pressures in the ovulatory, follicular, and luteal phases. Two, because arterial distensibility in our study was assessed only in the radial artery, the question as to whether the menstrual cycle also affects the mechanical properties of larger arteries with a more elastic and less muscular structure remains to be determined. Although the current inability to noninvasively obtain precise measurements of beat-to-beat blood pressure at or near the sites at which large-artery distensibility is derived makes this determination less precise, this is an obviously important question, because overall arterial distensibility depends more on large elastic than on middle-size arteries. Three, the variations of arterial distensibility during the menstrual cycle that we have observed represent the acute effect of physiological alterations in estrogens, progesterone, and other hormones on the arterial wall. This does not necessarily reflect the arterial effect due to chronic alterations of the estrogen-progesterone balance after menopause or after estrogen replacement therapy. However, recent observations indicate that in postmenopausal women, estrogen replacement therapy is accompanied by a systemic vasodilatation and an increase in arterial distensibility. Thus, we can suggest that the physiological effects of estrogens on arterial distensibility may not be different from the therapeutic long-term one.

References


